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ORIGINAL RESEARCH REPORT

# CD209-336A/G promotor polymorphism and its clinical associations in sickle cell disease Egyptian Pediatric patients

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CD209 A>G polymorphism;
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**Abstract**
*Objectives:* To detect the frequency of CD209 A>G polymorphism in sickle cell disease (SCD) Egyptian patients and to evaluate the use of CD209 A>G polymorphism as a genetic predictor of SCD clinical heterogeneity.
*Methods:* A total of 100 Egyptian children with SCD and 100 Egyptian controls were tested for CD209 A>G polymorphism and were followed up prospectively between June 2012 and December 2014.
*Results:* Comparison of CD209 A>G polymorphism among cases and controls did not show statistically significant difference ($p = .742$). In addition, comparison of the allelic frequency did not show statistically significant difference ($p = .738$). Infections occurred more frequently among the heterozygous genotype (AG; 60.5%) and homozygous genotype (GG; 75%) patients than among the wild (AA) genotype (24.1%; $p < .001$). The use of hydroxyurea treatment was significantly higher among the wild (AA) genotype (47%) than the heterozygous (AG; 21%) and homozygous (GG; 5%) genotypes ($p = .003$).

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*Conclusion:* We found no significant difference between our population of Egyptian SCD cases and controls regarding CD209 A>G polymorphism. Infections occurred more frequently among the heterozygous genotype (AG) and homozygous genotype (GG) patients.



## Introduction

Sickle cell disease (SCD) is an inherited red blood cell disorder, characterized by chronic hemolysis, vaso-occlusive complications, and progressive multiorgan damage, with a major impact on patients' life expectancy and quality of life [1]. More than 300,000 new cases of SCD are reported worldwide annually [2]. In Egypt, HbS carrier rates vary from 9% to 22% with a heterogeneous distribution [3].

Infectious complications are a leading cause of morbidity and mortality in patients with SCD. Several mechanisms are supposed to contribute to this susceptibility. The exact reasons for the propensity of sickle cell patients to infection are not clear and are still a matter of debate [4].

The human immune system attempts to control infection as soon as a pathogen begins to disrupt the physical and chemical barriers of innate immunity. This initial response is mediated by specialized cells that capture, process, and present microbial antigens to the effector cells of adaptive immunity. Dendritic cells (DCs) capture antigens in peripheral tissues and direct them to the lymph nodes. A receptor known as DC-specific *I*CAM-3-grabbing nonintegrin (DC-SIGN) recognizes and binds carbohydrates with high mannose content. Such carbohydrates are present in the external structure of certain pathogens, where they promote pathogen internalization and subsequent antigen presentation. In addition to its role in pathogen capture, DC-SIGN is involved in the migration of DCs and activation of T lymphocytes. The gene encoding DC-SIGN is known as CD209 and is located at 19p13.2. It is composed of seven exons and six introns, and is about 13 kb in length. One of the most well-studied single-nucleotide polymorphisms of this gene is a nucleotide transition from adenine (A) to guanine (G) at position −336 (−336A/G, rs4804803) in the promoter region of CD209 [5]. DCs play an important role in moderating the balance between tolerance and immunity [6,7]. They act as master regulators of acquired and innate immune responses [8]. DC-SIGN is a kind of newly discovered immune molecule with many functions: on the one hand, it could mediate DC migration, antigen internalization, and T-cell activation; on the other hand, it could be the target of certain pathogens or tumor cells, which may lead to escape of immune surveillance or immune suppression [9].

The role of CD209 in different inflammatory disorders has been studied, notably in juvenile idiopathic arthritis and Kawasaki disease [10,11]. The G allele of DC-SIGN promoter −336 (rs4804803) was found to be a risk allele in the development of Kawasaki disease in a Chinese population [12].

Inflammation is a cardinal component of the pathophysiology of SCD. The spectrum of SCD inflammation is broad, impacting many pathways in virtually all organ systems [13]. Interaction between vascular endothelium and sickle red blood cells leads to episodic microvascular occlusion, with consequent tissue ischemia and further reperfusion; these processes are characterized by severe vascular and inflammatory stress [14].

Because infectious complications are a leading cause of morbidity and mortality in patients with SCD, and to obtain data on the influence of CD209 on susceptibility to various infectious diseases and inflammatory disorders, we planned this study to detect the frequency of CD209 −336A/G polymorphism in Egyptian patients with SCD and to evaluate the use of CD209 −336A/G polymorphism as a genetic predictor of SCD clinical heterogeneity.

## Patients and methods

We designed a prospective cohort study, including 100 Egyptian patients with SCD and 100 Egyptian control participants of similar age and sex without significant medical history. The control participants were chosen from the population attending the general surgery clinic for elective surgical procedures with a normal complete blood count and negative family history of SCD.

The study protocol was in accordance with the local hospital research guidelines and written informed consent was obtained from all patients before study initiation. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Patients were diagnosed and followed in the clinical hematology unit of Cairo University Children Hospital. Diagnosis of SCD was based on hemoglobin electrophoresis and high-performance liquid chromatography (Bio-Rad, Hercules, California, USA). All patients were in steady state (i.e., they had no acute event for at least the preceding 4 weeks). All patients with SCD in our hematology clinic receive regular immunization against *Haemophilus influenzae* B, meningitis ACYW-135, and pneumococcal infection. They also receive chemoprophylaxis by either monthly long-acting penicillin or daily oral amoxicillin.

We excluded patients who received blood transfusion within the last 3 months prior to the study period and patients diagnosed to have any other chronic inflammatory condition (e.g., rheumatoid arthritis, osteoarthritis, or inflammatory bowel disease). All patients fulfilling the inclusion criteria were enrolled. The enrollment period was 3 months before the study period.

Patients were followed up prospectively between June 2012 and December 2014 to evaluate the relation between CD209 gene polymorphism and the frequency of complications of SCD, in the form of number of vaso-occlusive crisis (VOC) attacks, acute chest syndrome (ACS), renal injury,

and pulmonary hypertension. The average number of VOC per year as well as any attack of ACS was documented. VOC was defined as pain in the extremities, back, and abdomen without any other explanation [15]. ACS in SCD is defined as a new infiltrate on chest radiograph associated with one or more symptoms, such as fever, cough, hypoxia, tachypnea, or dyspnea [16]. Pulmonary hypertension was evaluated using echocardiography; it was defined as tricuspid regurgitant jet velocity >2.5 m/s [17]. The patients were assessed for early renal injury using albumin-to-creatinine ratio (A/C ratio), as microalbuminuria has been described as a preclinical indicator of glomerular damage in patients with SCD [18]. Other complications such as avascular necrosis or infections (defined as any infection necessitating hospitalization) were also recorded.

The use of blood transfusion as well as its frequency and the use of hydroxyurea (HU), including its dose and duration, were reported.

Routine laboratory investigations such as complete blood count, reticulocyte count, ferritin levels, bilirubin levels, and Albumin/Creatinine ratio (A/C) were reported.

### CD209 −336A/G (rs4804803) polymorphism genotyping analysis

Genomic DNA was extracted from 2 mL of peripheral whole blood mononuclear cells using QIAamp DNA Blood Mini Kit (Qiagen, Germany). DNA concentration was measured using Nanodrop ND-1000 (NanoDrop Technologies, Thermo-Fisher Scientific, DE) and samples were diluted to 10 ng/μL using nuclease-free water. Primers, probes, and TaqMan Universal PCR Master Mix were obtained from Applied Biosystems (Foster City, CA, USA). Genotyping of the CD209 gene polymorphism (rs4804803) was performed using TaqMan single-nucleotide polymorphism genotyping assays (Applied Biosystems). The primer sequences used were as follows: 5′-ACTGTGTTACACCCCCTCCACTAG-3′ (sense), 5′-AGGAAAG CCAGGAGGTCACA-3′ (antisense). The sequences of the TaqMan probes were 5′-CTACCTGCCCACCC-3′ and 5′-CTGCCTA CCCTTGC-3′. The probes were labeled with the fluorescent dyes VIC and FAM, respectively. DNA was amplified in a total volume of 20 μL containing 10 μL of TaqMan Universal Master Mix (2×; Applied Biosystems, Foster City, CA, USA), 1 μL of TaqMan Genotyping Assay mix (20×), 20-ng template DNA, and nuclease-free water. Polymerase chain reaction (PCR) was performed on StepOne Real-Time PCR (Applied Biosystems) using the following protocol: pre-PCR read at 60 °C for 30 s, holding stage at 95 °C for 10 min, 40 cycles of denaturing at 92 °C for 15 s, 40 cycles of annealing at 60 °C for 90 s, and post-PCR read at 60 °C for 30 s. After PCR amplification, allelic discrimination was done on StepOne Real-Time PCR system (Applied Biosystems). The fluorescent yield for the two different dyes was measured and presented in a two-dimensional graph.

### Statistical analysis

Data were statistically described in terms of mean ± stan dard deviation, median and range, or frequencies (number of cases) and percentages when appropriate. Odds ratio with the 95% confidence intervals were calculated of the genotypes and alleles between cases and controls. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples when comparing two groups and Kruskal−Wallis test when comparing more than two groups. For comparing categorical data, chi-square ($\chi^2$) test was performed. Exact test was used when the expected frequency is less than 5. All *p* values less than .05 were considered to be statistically significant. All statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

## Results

A total of 100 Egyptian children with SCD and 100 Egyptian control participants of similar age and sex were recruited for the study. Demographic data of cases and controls as well as clinical and laboratory data of cases are presented in Table 1.

Study of CD209 −336A/G polymorphism in cases and controls showed that the homozygous genotype (GG) had the least frequency among cases and was almost equally low among controls. Comparison of CD209 −336A/G polymorphism among cases and controls did not show statistically significant difference ($p = .742$). In addition, comparison of the allelic frequency did not show any statistically significant difference ($p = .738$; Table 2).

We compared the clinical and laboratory data of the patients carrying the three genotypes (AA, AG, and GG). There was no statistically significant difference between the clinical and laboratory data of the patients carrying the three genotypes apart from the occurrence of infections during the study period and the use of HU. Infections were significantly higher among the homozygous (GG) genotype (75%) and the heterozygous (AG) genotype (60.5%) than patients carrying the wild (AA) genotype (24.1%) ($p < .001$). The ages of the patients who had infections ranged from 2 years to 23 years with a mean of 10.95 years. The types of infections were pneumonia ($n = 25$ patients), gastroenteritis ($n = 7$), urinary tract infections ($n = 7$), and osteomyelitis ($n = 2$). All of these patients were treated with no subsequent complications.

The use of HU treatment was significantly higher among the wild (AA) genotype (87%) than the heterozygous (AG; 55.3%) and homozygous (GG; 62.5%) genotypes ($p = .003$; Table 3).

## Discussion

SCD is characterized by morphologically abnormal red cells, vaso-occlusion with ischemic tissue injury, and susceptibility to infection. Infections, such as pneumonia, osteomyelitis, meningitis, urinary infections, and septicemia, are a common cause of hospitalization in patients [19]. The severity of SCD varies greatly between individuals. While many patients have reduced splenic function, the mechanisms that render patients with SCD more susceptible to infection are unclear. Several lines of evidence indicated the association between CD209 and infectious diseases, such as dengue fever, tuberculosis, and AIDS [20−22].

**Table 1** Demographic, Clinical and Laboratory data of the patients and controls.

| | Cases | Controls | P value |
|---|---|---|---|
| M/F | 53/47 (53%/47%) | 51/49 (51%/49%) | 0.777 |
| Age (years) | 10.4 ± 4.3 | 11 ± 3.9 | 0.376 |
| | | | Cases |
| M/F | | | 53/47 (53%/47%) |
| Hb genotype | | Sβ | 34 (34%) |
| | | SS | 66 (66%) |
| Type of Pulmonary affection | | ACS | 18 (37.5%) |
| | | PHT | 30 (48%) |
| Avascular necrosis | | | 8 (8%) |
| CNS affection type | | Stroke | 4 (4%) |
| | | TIAs | 5 (5%) |
| Infections | | | 42 (42%) |
| Kidney Dysfunction | | | 48 (48%) |
| Blood transfusion | | | 82 (82%) |
| HU treatment | | | 73 (73%) |
| | | | Mean ± SD |
| Age (years) | | | 10.4 ± 4.3 |
| VOC (number/year) | | | 1.3 ± 1.3 |
| Frequency of blood transfusion (unit/ year) | | | 3.2 ± 2.7 |
| HU dose (mg/kg/day) | | | 18.9 ± 4.3 |
| HU duration (years) | | | 3.3 ± 3.1 |
| CBC | | Hb (g/dl) | 7.7 ± 1.5 |
| | | TLC ($\times 10^3/mm^3$) | 10.0 ± 4.4 |
| | | Plt ($\times 10^3/mm^3$) | 362.9 ± 171.6 |
| Reticulocytic count (%) | | | 8.5 ± 6.6 |
| Ferritin (ng/ml) | | | 1047.7 ± 1448.9 |
| Bilirubin (mg/dl) | | Total | 2.1 ± 0.9 |
| | | Direct | 0.3 ± 0.2 |
| A/C ratio (mcg/mg) | | | 401.6 ± 506.3 |

M/F: male/female, ACS: Acute chest syndrome, PHT: Pulmonary Hypertension, TIAs: transient ischaemic attacks, SD: Standard deviation, VOC: vasoocclusive crisis, HU: Hydroxyurea, Hb: Hemoglobin, TLC: Total leucocytic count, Plt: Platelets, A/C: Albumin/creatinine.

**Table 2** CD209 A>G Polymorphism & Allelic frequency among cases and controls.

| | | Cases | Controls | P value |
|---|---|---|---|---|
| CD209 A > G Polymorphism | AA | 54 (54%) | 54 (54%) | 0.742 |
| | AG | 38 (38%) | 35 (35%) | |
| | GG | 8 (8%) | 11 (11%) | |
| Wild allele (A) | | 146 (73%) | 143 (71.5%) | 0.738 |
| Mutatnt allele (G) | | 54 (27%) | 57 (28.5%) | |

Given the documented association of CD209 −336A/G polymorphism with disease susceptibility and the severity of clinical manifestations, studies of this variant in different populations are needed. We aimed, in this study, to detect the frequency of CD209 −336A/G polymorphism in Egyptian patients with SCD and to evaluate the use of CD209 −336A/G polymorphism as a genetic predictor of SCD clinical heterogeneity.

In this study, we found that only 8% of the SCD cases and 11% of the controls carried the homozygous genotype (GG). We also observed that the mutant allele G was present in 27% of cases and 28.5% of controls (Table 2). Our results showed no significant difference in CD209 −336A/G polymorphism between the SCD group and the control group ($p = .742$). In addition, comparison of the allelic frequency did not show statistically significant difference ($p = .738$; Table 2). Noble et al. [23] found similar observation on comparison of African-American patients with SCD and healthy controls, but contrastingly, they found significant difference in genotypic and allelic frequencies of the homozygous mutant variant in African SCD and healthy controls, respectively. They showed a higher frequency of the homozygous genotype (GG) among African SCD cases (23.4%) and African-American cases (16.9%), but GG was almost absent among white patients (3.2%) [23]. Our observations, thus, showed that our population of SCD cases as well as controls had a much lower frequency of the homozygous genotype (GG) than African SCD cases and African-American SCD

**Table 3** Clinical and laboratory data of the patients classified according to CD209 A>G Polymorphism result.

| | | CD209 A > G Polymorphism | | | P value |
|---|---|---|---|---|---|
| | | AA N = 54 | AG N = 38 | GG N = 8 | |
| Sex | M/F | 26/28 | 21/17 | 6/2 | 0.343 |
| Hb genotype | Sβ/SS | 18/36 (33.3/66.7%) | 14/24 (36.8/63.2%) | 2/6 (75/25%) | 0.804 |
| Pulmonary affection | | 25 (46.3%) | 20 (52.6%) | 3 (37.5%) | 0.690 |
| Type of Pulmonary affection | ACS | 7 | 11 | 0 | 0.068 |
| | PHT | 18 | 9 | 3 | |
| Avascular necrosis | | 4 (7.4%) | 4 (10.5%) | 0 | 0.591 |
| CNS affection | | 7 (13%) | 2 (5.3%) | 0 | 0.290 |
| CNS affection type | Stroke | 2 | 2 | 0 | 0.073 |
| | TIA | 5 | 0 | 0 | |
| Infection | | 13 (24.1%) | 23 (60.5%) | 6 (75%) | <0.001 |
| Kidney Dysfunction | | 27 (50%) | 18 (47.4%) | 3 (37.5%) | 0.800 |
| Blood transfusion | | 44 (81.5%) | 31 (81.6%) | 7 (87.5%) | 0.915 |
| Hydroxyurea treatment | | 47 (87%) | 21 (55.3%) | 5 (62.5%) | 0.003 |
| Age | | 10.69 ± 3.69 | 9.89 ± 5.35 | 12 ± 3.38 | 0.288 |
| VOC | | 1.35 ± 1.33 | 1.37 ± 1.30 | 1.75 ± 1.90 | 0.775 |
| Frequency of blood transfusion (unit/ year) | | 3.57 ± 3.09 | 2.87 ± 2.43 | 3.14 ± 1.78 | 0.406 |
| HU duration (years) | | 3.22 ± 3.28 | 3.12 ± 2.72 | 5.80 ± 3.70 | 0.110 |
| | A2 | 2.46 ± 1.26 | 2.35 ± 0.88 | 2.04 ± 0.29 | 0.351 |
| CBC | Hb (g/dl) | 7.75 ± 1.64 | 7.61 ± 1.36 | 7.81 ± 1.31 | 0.862 |
| | TLC ($\times 10^3/mm^3$) | 9.98 ± 4.44 | 10.28 ± 4.54 | 8.93 ± 4.12 | 0.543 |
| | Plt ($\times 10^3/mm^3$) | 380.09 ± 200.16 | 343.89 ± 121.88 | 338.25 ± 173.35 | 0.717 |
| Reticulocytic count (%) | | 8.58 ± 6.80 | 8.17 ± 6.97 | 9.50 ± 4.63 | 0.240 |
| Ferritin (ng/ml) | | 1263.55 ± 1832.78 | 732.92 ± 621.10 | 1086.50 ± 1149.15 | 0.602 |
| Bilirubin (mg/dl) | Total | 2.36 ± 1.07 | 1.91 ± 0.65 | 1.90 ± 0.69 | 0.816 |
| | Direct | 0.40 ± 0.31 | 0.31 ± 0.13 | 0.35 ± 0.15 | 0.273 |
| A/C ratio (mcg/mg) | | 451.48 ± 627.24 | 345.04 ± 317.83 | 334.56 ± 268.63 | 0.794 |

M/F: male/female, Hb: Hemoglobin, ACS: Acute chest syndrome, PHT: Pulmonary Hypertension, TIAs: transient ischaemic attacks, VOC: vasoocclusive crisis, HU: Hydroxyurea, TLC: Total leucocytic count, Plt: Platelets, A/C: Albumin/creatinine.

cases, but a higher frequency than white patients, as shown in the findings of Noble et al. [23].

Extensive studies in different populations have shown a low genotypic frequency of the homozygous genotype (GG). A genotypic frequency of 5%, 1%, and 3% was shown in a Thai study conducted among three groups of healthy control populations [24]. Further studies in Taiwanese, general Brazilian, and Sao Paulo populations showed genotypic frequency of 0%, 3%, and 5%, respectively [25–27].

Our study, therefore, confirms that despite the insignificant difference between cases and controls regarding CD209 −336A/G polymorphism, there is genetic heterogeneity among different populations.

In patients with SCD, several mechanisms are supposed to contribute to susceptibility to infectious complications, a major factor being the early loss of splenic function. Other mechanisms have been investigated including the polymorphism of the gene encoding the Fc receptor (FcγRIIA) [28], the polymorphism of the gene encoding the mannose binding protein [29], and the polymorphism of the human leukocyte antigen system [30] and the gene encoding the myeloperoxidase [31]. Moreover, our studied polymorphism has been linked to susceptibility to infections [32]. In our study, the wild-type and heterozygous variants (AA and AG) were found in 54% and 38% of cases, and 54% and 35% of controls, respectively (Table 2). Serious infections occurred in 24.1%, 60.5%, and 75% of the AA, AG, and GG groups, respectively (Table 3). This showed that there was a significant association between infections and the homozygous genotype (GG; $p < .001$) (Table 3). This confirms the observation shown by previous studies conducted in different populations and demonstrated an association between CD209 −336A/G polymorphism and susceptibility to a variety of diseases, notably infections [25,33,34]. Thus, our results confirm that CD209 −336A/G polymorphism can be used as a predictor of the occurrence of infections among SCD populations.

The use of HU treatment was significantly higher among the wild (AA) genotype (87%) than the heterozygous (AG; 55.3%) and homozygous (GG; 62.5%) genotypes ($p = .003$). This could be explained by the fact that patients with the wild (AA) genotype had the highest percentage of SS disease (66.7%), compared with those in the heterozygous (AG; 63.5%) and homozygous (GG; 25%) genotypes (Table 3). However, most of our patients were on HU treatment, irrespective of their sickle genotype.

## Conclusion

To our knowledge, this is the first study to investigate the association of CD209 −336A/G polymorphism with clinical and laboratory profiles of Egyptian patients with SCD. We conclude that there is no significant difference between our population of Egyptian SCD cases and controls regarding CD209 −336A/G polymorphism. Infections occurred more frequently among the heterozygous genotype (AG) and homozygous genotype (GG) patients ($p < .001$). One of the limitations to this study is the lack of identification of the causative organisms of infections. Another limitation is the relatively short period of follow-up to detect major SCD complications such as infections, VOC, and ACS. Therefore, we intend to publish an update in 5 years' time.

Our conclusions suggest that the genotypic frequency of CD209 −336A/G polymorphism varies among different ethnic populations. However, CD209 −336A/G polymorphism can be used as a predictor of susceptibility to infections in patients with SCD. Further studies to detect the associations of different pathogens to CD209 −336A/G polymorphism genotypes in patients with SCD and to confirm our results are needed.

## Conflicts of interest

The authors have no conflict of interest to declare.

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